Medical Staff Conference

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Wegener's Granulomatosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been a tradition at this institution to ask our chief medical residents to present the Medical Staff Conference before their departure. Today Dr. David S. Gullion will discuss Wegener's granulomatosis.*

DR. GULLION:† Wegener's granulomatosis is a curious clinical-pathological complex of unknown cause. In 1931, Klinger[1] reported a patient who died in uremia with severe destructive sinusitis, nephritis and disseminated vasculitis. The anatomical pathologic features were particularly interesting in that they included numerous splenic granulomata, generalized arteritis and a glomerular lesion. A few years later, Wegener[2] reviewed three cases and was able to define this disease as a distinct clinical and pathological entity. He held the view that it was probably a unique variety of periarteritis nodosa. Because nasal involvement was present in most of his patients, he coined the phrase "rhinogenic granuloma."

Interest in this disease was revived almost twenty years later at Columbia University in the Departments of Medicine and Surgical Pathology. Godman and Churg[3] presented data from seven additional patients and established the pathological criteria for Wegener's granulomatosis. In conjunction with their publication, Fahey[4] presented the clinical aspects of the disease. These investigators emphasized that it is a distinct syndrome that is well characterized both clinically and anatomically. Clinically, the diagnosis may be suggested by a recurrent respiratory tract inflammation, particularly when associated with renal abnormalities. The pathological findings were consistent and allowed the establishment of certain criteria: (1) necrotizing granulomatous lesions in the upper air passages (nose, paranasal sinuses, nasopharynx, glottis, or adjacent regions) or in the lower respiratory tract (trachea, bronchi, lungs) or in both; (2) generalized focal necrotizing vasculitis, involving both arteries and veins, almost always in the lungs, and more or less widely disseminated in other sites; and (3) glomerulitis, characterized by necrosis (and thrombosis) of loops or lobes of the capillary tuft, capillary adhesions, and evolution as a granulomatous lesion.[3]

Some interesting characteristics of their patients were noted: severe destructive necrosis of the larynx and nasal and paranasal structures; coagulative necrosis of the spleen, which often was enlarged; aseptic necrosis of two-thirds of the mitral

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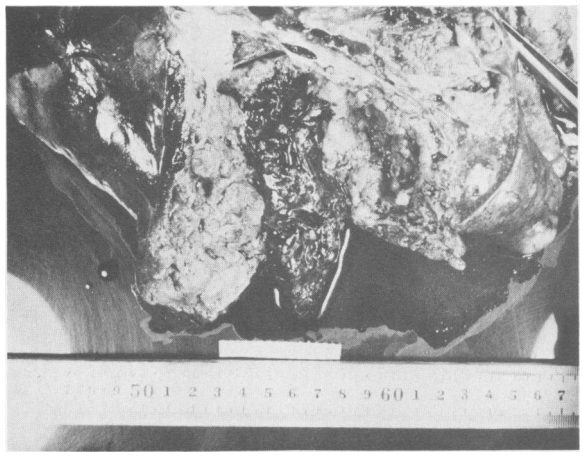

Figure 1.—Necrosis and infection of lung in Wegener's granulomatosis.

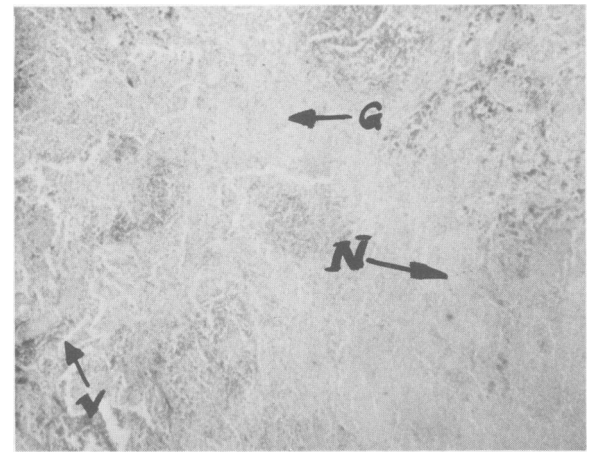

Figure 2.—Microscopic picture of caseating granulomatous tissue demonstrating a granuloma (G), necrosis (N) and vasculitis (V).

valve leaflet and chordae; involvement of the coronary arteries with severe arteritis and, in all cases, involvement of the kidneys which showed characteristic fine punctate hemorrhages on the surface and glomerulitis on microscopic evaluation.

Some of these findings are reviewed in the figures. Figure 1 shows the gross anatomical picture of the disease in the lung. Noticeable are the large areas of necrosis and inflammatory masses which are numerous and frequently near the pleura. The necrotic aspects are well demonstrated by circumscribed white-yellow lesions. The center of these nodules is usually soft, friable and varies from reddish-yellow to greenish-brown. The large area of infarction, which is hemorrhagic, was most likely caused by the occlusion of pulmonary arteries supplying the area. In Figure 2 with the aid of a microscope we see through an area of necrotic, caseating, granulomatous tissue. Present are swirls of epithelial cells which are typical of granuloma formation. Figure 3 shows the acute necrotizing arteritis which is present in the pulmonary arteries. The artery shown is relatively large, but small arteries are more consistently involved in this process. We can see infiltration of the media by numerous mononuclear cells, and with an elastic stain one can observe disruption of the normal elastic structures of the arterial wall. A consistent pathological finding in the cases presented in the literature has been involvement of the pulmonary arteries.

The kidneys, as already mentioned, showed fine punctate hemorrhages on the surface. Viewed microscopically there was a characteristic focal necrotizing glomerulitis with fibrin thrombi and focal necrosis of glomerular tufts. Figure 4 shows a typical granuloma within the medullary portion of the kidney.

Differential Diagnosis

As will be discussed later, Wegener's granulomatosis presents in a variety of ways. These range from a very limited form to the overwhelmingly fulminant vasculitis with death in uremia. In the recent review by Fauci and Wolff,[5] the range of differentiation extended from diseases that are predominantly vasculitic to those that are definitely granulomatous. Classic periarteritis nodosa is a widespread vasculitis which is usually confined to medium-sized arteries and predominantly involves the bifurcation or branching of those arteries. The distal smaller vessels are usually only involved by extension or because of thrombosis. Otherwise, in periarteritis nodosa the small arteries and veins are spared, in contrast to the findings in Wegener's granulomatosis. There is renal damage in periarteritis, but usually not the focal necrotizing glomerulitis seen in Wegener's granulomatosis. Similarly, hypertension, which is so common in periarteritis, is rarely seen in Wegener's granulomatosis. Pulmonary vasculitis is uncommon in periarteritis nodosa (PAN) but, as mentioned, was found in every reported case of Wegener's. The systemic pulmonary arteries, namely bronchial vessels, however, are involved with the diffuse vasculitis in PAN. Finally, necrotizing granulomata are not a feature of periarteritis.

Moving away from the classic periarteritis, we have the microscopic form of periarteritis nodosa

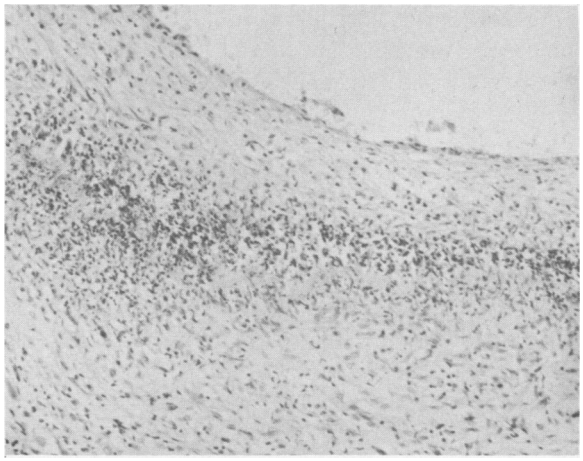

Figure 3.—Acute necrotizing arteritis of pulmonary artery. Infiltration with mononuclear cells is shown.

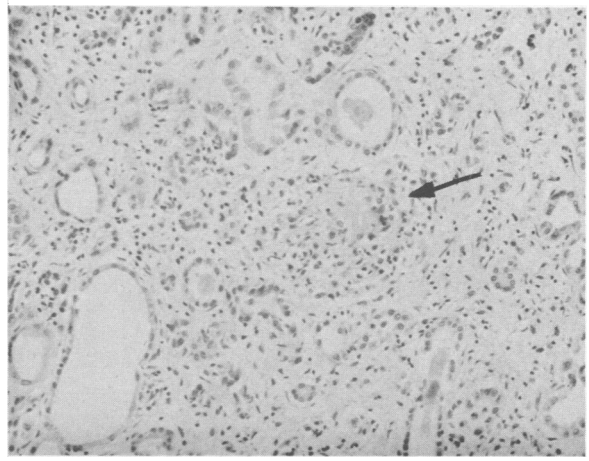

Figure 4.—Granuloma (arrow) in medullary portion of kidney from patient with Wegener's granulomatosis.

as described in the earlier literature, or what more recently has been designated by Zeek[6] as hypersensitivity angiitis. In the late 1940's and early 1950's Zeek described and reviewed hypersensitivity angiitis and periarteritis nodosa. Hypersensitivity angiitis is an acute necrotizing inflammation involving the small arterioles and veins, much as Wegener's granulomatosis does. The pulmonary vessels are frequently affected. The extravascular lesions in the spleen and kidney are also similar to those found in Wegener's granulomatosis. The differentiating point, however, is a frequent history of drug antigen being introduced shortly before the onset of symptoms. Most patients with this condition have had allergic reactions to sulfonamides. Pathologically, the distinguishing feature here is that all of the lesions of hypersensitivity angiitis appear to be in the same stage of involvement, in contrast to Wegener's granulomatosis in which the lesions are a combination of acute vasculitides in all stages of healing. Furthermore, granulomatous formation with necrosis is not a feature of hypersensitivity angiitis.

Continuing through the list of predominantly vasculitic diseases, there is systemic lupus erythematosus, scleroderma, dermatomyositis, Sjögren's syndrome, rheumatoid arthritis with arteritis and giant cell arteritis. In none of these disease processes does one find the classic triad of necrotizing granulomata, vasculitis of the upper and lower respiratory tract, and glomerulitis. Thus far none of the studied cases that have satisfied the established criteria of Wegener's granulomatosis has shown an abnormal serological pattern. Thus, by this criterion, one can frequently distinguish these other vasculitides from Wegener's. In the cases studied there has been no appearance of lupus erythematosus cells, antibodies directed to native double stranded deoxyribonucleic acid (DNA), single stranded DNA, ribonucleic acid (RNA), or mixtures of DNA with the nuclear proteins. There also has not been a detectable antinuclear antibody that reacts with a combination of nuclear material including histones, DNA and other nuclear substances.

Henoch-Schönlein purpura is a syndrome, usually found in children and adolescents, that involves the joints, gastrointestinal tract and kidneys. There is often widespread purpura, which reflects the pathogenic process of damage to the endothelium of small vessels. The presentation frequently includes abdominal pain, nausea, vomiting, diarrhea and hemorrhage. The renal lesion is usually focal and does not progress to renal failure. Again, the phenomenon appears to be allergic in origin and the lesions are usually of the same crop.

Continuing in the differential diagnosis, there are other diseases which have mixed granulomatous and vasculitic properties. Churg and Strauss[7] described "allergic angiitis and granulomatosis." Included in this group is the characteristic clinical syndrome of asthma, fever and hypereosinophilia.[8] The anatomical findings were very similar to Wegener's granulomatosis but differed in that the patients had severe asthma, there was pronounced although not persistent peripheral eosinophilia, there was a strong tendency toward cardiac involvement, and the respiratory tract lesions were less extensive and less aggressive. A variety of diseases with pulmonary infiltrations and eosinophilia (the PIE syndromes) may have aspects similar to

TABLE 1.—*Clinical Characteristics of Patients with Wegener's Granulomatosis*

Male : Female	3 : 2
Age Range	3 mos. to 75 yrs.
Peak	4th to 5th decade
Mean	44 yrs.

Symptoms	*Percent Cases*
Previously healthy persons	
Rhinorrhea and sinus pain	94
Fever	80
Anorexia, weight loss	80
Cough	60
Chest pain	60
Arthralgia/arthritis	60/20
Skin lesions	50
Otitis media	40
Ocular lesions	40
Hemoptysis	20
Neurological symptoms	20-50

Wegener's but do not involve the kidney and do have eosinophilia, which is uncommonly seen in Wegener's granulomatosis.

The granulomatous diseases that must be included in the differential diagnosis include the infectious, as well as the noninfectious ones (or those granulomatous diseases for which causes have not been identified). We can briefly eliminate the infectious cause by either culturing or observing the organism, and corroborating the diagnosis by serological tests with or without positive cellular immunity to the infectious agent. These diseases include tuberculosis, histoplasmosis, blastomycosis, coccidioidomycosis, syphilis, tularemia and lymphogranuloma venereum.

Sarcoidosis, although involving the pulmonary structures, may be easily differentiated on pathological grounds because of the non-caseating or non-necrotic aspects of the granulomata and the absence of vasculitis. Berylliosis produces pulmonary lesions very similar to sarcoidosis, but there is no other widespread involvement such as is seen in Wegener's granulomatosis. Usually there is a history of exposure to beryllium. Last, within the granulomata group we have the very rare and unusual lethal midline granuloma.[9] This is a poorly understood entity with destructive lesions of the midline upper respiratory tract structures, especially the nose, sinuses, palate and pharynx. This entity has also been described as agnogenic progressive lethal granulomatous ulceration of the nose and face or granuloma gangraenescens. There definitely is overlap of this syndrome with Wegener's granulomatosis. Pathologically disseminated visceral granulomata are present, at times even with occasional necrotizing angiitis. Glomerulitis, however, was not found in any case, and none of the patients died in renal failure. Some feel lethal midline granuloma is a variant of Wegener's granulomatosis.

The first of other pulmonary renal syndromes is the well known Goodpasture's syndrome, which is characterized by pulmonary hemorrhage and glomerulonephritis. The pulmonary hemorrhage is probably the most striking phenomenon distinguishing Goodpasture's from Wegener's; 98 percent of patients with Goodpasture's present with pulmonary hemorrhage. In addition, the diagnosis can be firmly established by the finding of antiglomerular basement membrane antibodies by immunofluorescence in a renal biopsy specimen. The pulmonary lesions are thought to be a reaction of the anti-basement membrane antibody with those basement membranes of the alveolar septal membranes. On immunofluorescence a very fine linear deposit is seen. This linear deposition is due to the interaction of the basement membrane with the antibody itself as opposed to an immune complex glomerulonephritis in which the immune complexes are filtered at the glomerulus and appear as a coarse, granular deposit along the basement membrane. This type of deposition is not specific and, in fact, has also been found in a few cases of Wegener's granulomatosis. Streptococcal infections of the upper respiratory tract and pneumonia with glomerulonephritis can be differentiated on culture, as well as on serological grounds.

To complete the differential diagnosis, neoplastic diseases should be considered because of their location. Nasopharyngeal lymphoma and sarcomas, midline malignant reticulosis, primary metastatic lung disease, Hodgkin's disease and lymphoma involving the lung all may resemble Wegener's because of the granulomatous reaction and necrosis associated with the neoplastic tissue. A few reports in the literature have made note of so close a resemblance of the biopsy specimen seen in Wegener's to that in neoplasia that a diagnosis of Hodgkin's disease was seriously entertained. Some of the bizarre cells seen in Wegener's may resemble Reed-Sternberg cells or even those of a reticulum cell sarcoma.

Clinical Characteristics

The clinical characteristics of Wegener's granulomatosis are presented in Table 1. The ratio of males to females is about 3 to 2, and in Fauci's series it was 11 to 7. The age range of patients

is from three months to 75 years, with a peak incidence in the fourth and fifth decades and a mean age of 44 years. The typical clinical presentation is with discomfort or complaints referrable to the upper respiratory tract. The complaints may be those of severe rhinorrhea, a nasal mucosal ulceration and sinus pain or drainage. These symptoms often wax and wane over months to years before the more fulminant aspects of the disease appear. In fact, renal involvement before nasal or sinus complaints is particularly unusual. Associated with this may be the involvement of the pulmonary structures leading to cough, pleuritic chest pain, abnormal chest x-ray studies, and hemoptysis. The latter occurs in up to 22 percent of cases. The presenting signs and symptoms in patients may be varied but usually revolve around the respiratory tract. However, the patient may present with skin ulcerations, joint symptoms, ocular manifestations or recurrent middle ear problems. Anorexia, malaise, fever and weight loss are all constitutional symptoms which frequently are found early in the course of disease. The clinical presentation is varied, and as mentioned, overlaps many other diseases.

Systems Involved in Wegener's Granulomatosis

For an appreciation of the wide spectrum of disease I will present the system involvement and describe some of those abnormalities found in patients with Wegener's granulomatosis. The eyes may be involved in up to 40 percent of cases. The ocular lesions reported include corneo-scleral ulceration, necrogranulomatous keratitis, granulomatous sclero-uveitis and conjunctivitis with occasional proptosis and pseudotumor of the orbit. In a series at the National Institutes of Health,[5] conjunctivitis, episcleritis and corneal ulceration, retinal artery thrombosis and proptosis were seen, and one patient had severe scleromalacia perforans.

About one third of patients with Wegener's granulomatosis have ear involvement, usually manifest by recurrent middle ear inflammation and pain.

Cutaneous involvement has been reported in up to 50 percent of patients. The lesions usually seen are those associated with the thrombosis of arteries and necrotizing angiitis. This leads to necrosis and ulceration of the skin. Subcutaneous nodules have also been reported, as have necrotizing papules of the finger tips.

Muscle involvement is uncommon and usually seen only as a perivascular infiltration. True myositis has not been a feature of this disease.

There are frequent complaints of arthralgias, but true arthritis is not common. The joint symptoms are usually transient and do not play a major role in the presenting symptoms or in the overall course.

As was mentioned before, there is a report of necrosis of the mitral valve with infiltration of mononuclear cells without evidence of bacterial infection.[3] The involvement of the coronary arteries is not frequent but may be associated with life-threatening, refractory arrhythmias and actual myocardial infarction with necrosis. Occasionally pancarditis is seen. In the series of Fauci and Wolff,[5] the heart was involved in five of seventeen patients. Three had pericarditis and, of these, one died of pulmonary hemorrhage. Two other patients died of intractable arrhythmias, and the autopsy on one confirmed severe vasculitis of the anterior descending branch of the left coronary artery.

As with many other systemic diseases, the nervous system is involved in a significant proportion of cases of Wegener's granulomatosis—reports put the incidence between 25 and 50 percent. Drachman[10] described the lesions as being of three types: (1) contiguous involvement from a destructive granulomatous process of the sinuses which involved the orbit and surrounding structures; (2) remote granulomatous lesions of the meninges or intracerebrally; and (3) a more generalized vasculitis of the nervous system which may be clinically very similar to that seen in lupus erythematosus. Specifically, the vasculitis may be associated with cerebrovascular occlusions, intracerebral or subarachnoid hemorrhages, polyneuritis or a mononeuritis multiplex such as is seen in periarteritis nodosa. The mononeuritis multiplex is not an infrequent finding in this disorder.[11]

Respiratory tract involvement, as has been emphasized here, is a cardinal feature of Wegener's granulomatosis, and the diagnosis should probably not be made unless there is such involvement. Mucosal ulcerations, septal perforations, saddle nose deformities from the destruction of the cartilaginous and bony portion of the nose, and various degrees of sinusitis are the most common findings. Secondary bacterial infection may be present in more than half the patients with sinus involvement. The lungs are almost invariably involved,

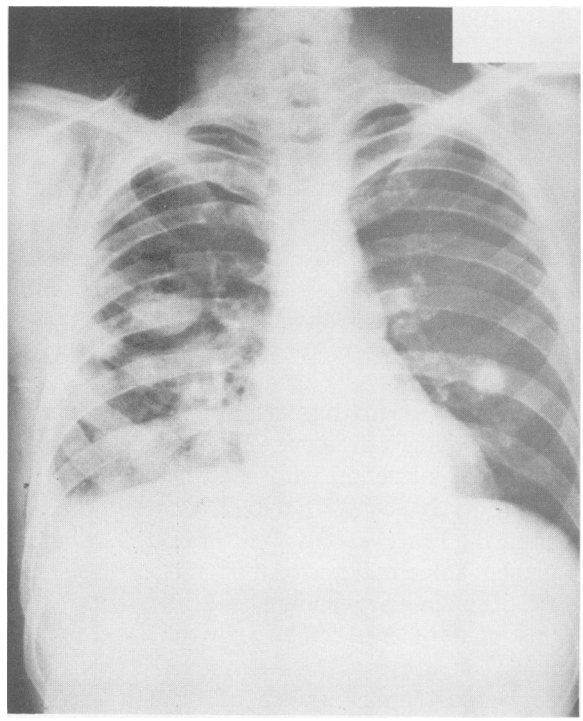

Figure 5.—Pulmonary nodules in Wegener's granulomatosis.

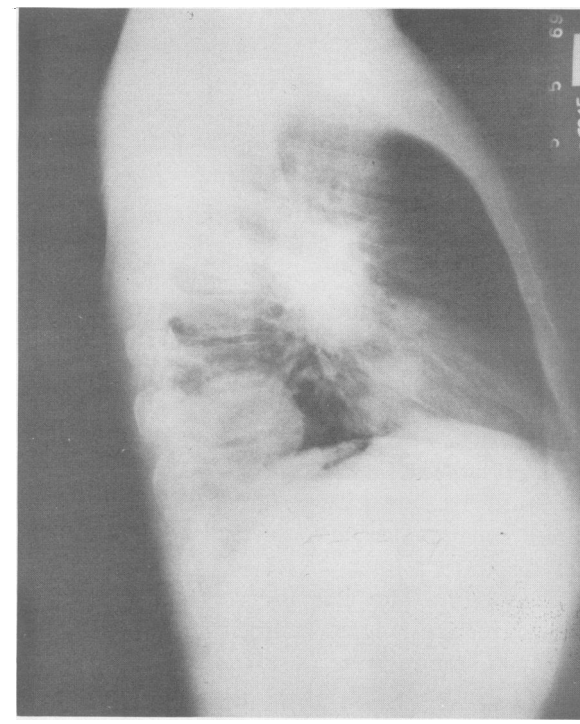

Figure 6.—Lateral view showing pleural involvement by nodules.

but have no characteristic lesion. Commonly seen are solitary or multiple nodular densities (Figures 5 and 6), or ill-defined infiltrates (Figure 7) which may vary in size and characteristics, from small coin-like lesions to large bilateral infiltrates. The occurrence of cavitary formation is becoming more frequently reported, with thick-walled cavities being most common and usually accompanied by surrounding inflammatory reaction. However, thin-walled cavities, characteristic of coccidioidomycosis, may be seen in up to 30 percent of patients with cavities. The pulmonary symptoms vary but usually consist of a low-grade persistent cough and some mild chest discomfort or pleuritic pain. Occasionally they may be of a more severe nature, with fulminant respiratory failure.

Finally, the renal involvement is the dreaded complication in generalized Wegener's granulomatosis. The prognosis is grave when renal damage is present, and there is frequently rapid progression to death due to renal failure. The urinary abnormalities of proteinuria, hematuria and red-blood-cell casts may be present for a number of weeks, but once there is functional impairment, the renal disease does not spontaneously arrest or regress.[4] As was mentioned before, the most common finding is a focal necrotizing glomerulitis not unlike that seen in subacute bacterial endocarditis and certain forms of periarteritis nodosa. Associated with this glomerulitis are various stages of healing, including hyalinization, adhesions and crescent formation. As we shall discuss later, the greatest benefit of therapy is control of the progression of the renal lesion. The long-term survival is directly contingent upon the degree of renal impairment. Fortunately, hypertension is not a problem in patients with Wegener's granulomatosis and in the most recent review[5] was not found at all.

In 1966 Carrington and Liebow[12] described 16 patients with a limited form of Wegener's granulomatosis. There was frequent upper and lower respiratory inflammation with concomitant symptoms. Abnormal chest x-ray studies were found in all cases, frequently raising suspicion of a neoplasm. Systemic manifestations were present—weight loss, fever, malaise and accelerated erythrocyte sedimentation rate—as were extrapulmonary lesions. There have been further reports of the limited form of Wegener's granulomatosis and the characteristic finding is the absence of the renal damage.[12,13]

Laboratory Findings

There is nothing specific in laboratory findings to confirm or deny the diagnosis of Wegener's

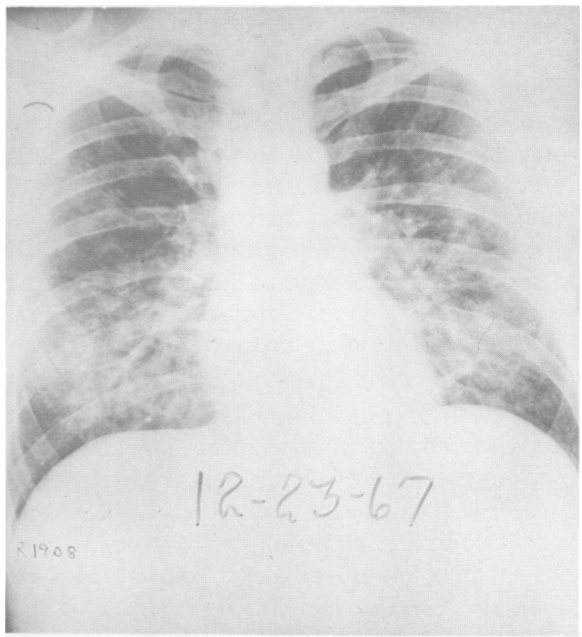

Figure 7.—Bilateral nodular perihilar infiltrates.

TABLE 2.—*Types of Therapy Used in Treating Wegener's Granulomatosis*

Antibiotics	
Radiotherapy	
Adrenocorticoids	
Cytotoxic Agents	*Toxicity*
1. Nitrogen mustard ..	Bone marrow depression
2. Methotrexate	Bone marrow depression; liver, GI, abnl.
3. Chlorambucil	Bone marrow depression
4. Azathioprine (1-2mg/kg/day) ..	Immunologic suppression Bone marow depression ↑Incidence malignant tumors
5. Cytoxan (1-2mg/kg/day) ..	Immunologic suppression Bone marow depression Incidence malignant tumors Hemorrhagic cystitis Azoospermia Ovarian destruction
Heparin (30-40,000 units/day)	Hemorrhagic complications

granulomatosis. Again, the combination of clinical, laboratory and pathological data must be used to make the diagnosis. Anemia is common; it is usually normocytic and normochromic without morphologic abnormality of red cells. Bone marrow examination usually shows only a mild erythroid hyperplasia without abnormal cells. Microangiopathic hemolytic anemia has been found in a few cases.[14] Its exact cause is unclear but most likely it is related to either splenic disruption of cells by fibrin strands or by the glomerular lesion which, at times, is associated with fibrin deposition with or without thrombosis of capillary tufts. Often there is a mild leukocytosis but specifically without eosinophilia. Interestingly, in the National Institutes of Health series,[5] seven out of eighteen patients had a platelet count greater than 400,000 per cu mm. There were no patients with platelet counts less than 150,000 per cu mm. There may be an acceleration of the sedimentation rate, and the mean value in the reported series is approximately 90 mm in one hour.

Treatment

The therapeutic approaches used in treating Wegener's granulomatosis have been many and varied (Table 2), probably owing to the uncertainty about what causes the tissue effects. None of the previous methods have been successful; and, therefore, the current approach in the management of patients with Wegener's granulomatosis is to treat the tissue inflammatory response and the immunological system which may be contributing to the pathogenesis in some as yet unknown way. Antibiotics were used consistently in the past few decades. When secondary infection occurred, as it did in approximately 40 percent of patients, antibiotics often were effective in reducing the acute infection. However, their use for treatment of underlying disease is not efficacious. Radiotherapy of local granulomatous lesions has been used often, and in some cases regression of the treated lesions has followed. However, one must keep in mind that regression may occasionally occur without treatment of any kind. Corticosteroids have been widely used in treating this disease. The effect has been unpredictable or unsuccessful, and renal involvement has progressed in all cases in spite of continued steroid therapy. The frustration with the therapy in Wegener's granulomatosis is attested by Fahey's seventh case.[4] After treatment with large doses of adrenocorticotropic hormone (ACTH) became less effective, "radiotherapy, thiethylene melamine, stilbesterol, testosterone and snake venom produced no change." Nitrogen mustard then was given, with a transient effect.

Because the prognosis of Wegener's granulomatosis is so poor, with an average life span of five months and mortality of 93 percent in two years,[15] there has been increasing interest in the use of cytotoxic agents in treatment. In 1954 and

during the following few years, nitrogen mustard was given a trial in some isolated patients. Following this, McIlvanie,[16] in 1966, reported upon a patient with the limited form of Wegener's granulomatosis who received chlorambucil with a successful response.

The following year Hollander and Manning[17] reported a case in which nitrogen mustard was given intravenously and then chlorambucil by mouth, with good response of a severe renal lesion. By 1971 there was increasing agreement that cytotoxic agents were beneficial in treating this disease, and increasing numbers of reports began to appear showing the efficacy of a variety of cytotoxic agents with emphasis on azathioprine and cyclophosphamide (Cytoxan®). Novack and Pearson[18] presented four patients who received cyclophosphamide (usually orally) with apparent regression of the lesions in all the patients. In these patients, steroids were either not used concomitantly or the doses of them were being tapered rapidly during the period of observation.

It is the current feeling of Fauci and Wolff[5] that cyclophosphamide or azathioprine should be started at the dose of 1 to 2 mg per kg of body weight per day by mouth and that the patient's clinical course should be monitored with frequent blood cell counts and renal function studies, including urinalysis. The institution of corticosteroid therapy at a dose of 40 to 60 mg of prednisone per day should be limited to those times when the constitutional symptoms or inflammatory vasculitic process are rampant. The two important toxic manifestations of cyclophosphamide need to be kept in mind: The hemorrhagic cystitis may occur either acutely or after many months of oral therapy. The bladder fibrosis and chronic inflammation is particularly disturbing. In addition, there is now increasing awareness of the effects of cyclophosphamide and other cytotoxic agents upon the reproductive organs, specifically, azoospermia and ovarian destruction.

I should mention two reports describing the use of heparin in the treatment of Wegener's granulomatosis. The rationale for its use originates from the fact that fibrin deposition in the glomerular capillary tufts is occasionally seen, with or without thrombosis. Roback[19] described a child with Wegener's granulomatosis who was treated with heparin and azathioprine. It was felt that the dramatic response of the renal insufficiency was due to the institution of heparin therapy. Likewise, Whitaker[20] presented a case of Wegener's granulomatosis with renal involvement that was treated with a combination of heparin and azathioprine with similar results.

In patients with the limited form of Wegener's granulomatosis the exact timing of therapy needs to be handled on an individual clinical basis. The pulmonary insufficiency may be of a great magnitude and require cytotoxic therapy. However, if the symptoms are low-grade and the disability not severe, the patient may not necessarily have an indication for cytotoxic therapy.

How long to continue therapy has not been established. As general outlines, it is necessary to keep in mind that with significant pulmonary and renal involvement the disease is uniformly fatal. If there is good control of the disease, then a one-year unequivocal remission would probably warrant tapering and stopping of therapy at that time. If the disease continues to smolder without definite remission, continued oral therapy may be indicated. The renal abnormalities should guide one as to the necessity of continued therapy.

Trade and Generic Name of Drug

Cytoxan® ..... cyclophosphamide

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